REMARKS/ARGUMENTS

Claims 1–39 are pending in the captioned application. Claims 1–14 are currently under examination, and claims 15–39 stand withdrawn from consideration.

The Examiner has rejected claims 1 and 10–13 under 35 U.S.C. § 102(b) as "being anticipated by Monforte et al (US 5,830,655, November 3, 1998)".

Specifically, the Examiner states, "Regarding claim 1, teach an assay comprising contacting a target nucleic acid with a oligonucleotide immobilized on an array, under conditions that allow hybridization, said target nucleic acid having at least one phosphorothioate moiety..." and, "Regarding claim 10 and 12, Monforte et al teach the method of claim 1, wherein at least one nucleotide is a ribonucleotide or is a deoxynucleotide..."

The Examiner further states, "Regarding claims 11 and 13, Monforte et al teach the method of claims 10 or 12, wherein the target nucleic acid comprises from up to four different thiodeoxyribonucleotides. The reference also teaches the use thio- modified nucleosides...The reference further inherently implies the use of thio-ribonucleotides in the teaching of the target comprising RNA..."

The Examiner concludes, "Therefore, Monforte et al meets the limitations of claims 1, 10–13 of the instant invention".

In response, Applicants respectfully assert that the methodology of the instant invention is quite different from that disclosed in the '655 patent, inasmuch as the instant methodology is related to an expression assay whereas the '655 patent is related to methodology to provide "more useful sizing and sequence information per fragment than extension products containing the entire primer" (see e.g., the Abstract). To emphasize the differences, Applicants have amended Claim1, upon which Claims 2-13 ultimately depend, to be in Jepson format; this claim, Applicants respectfully submit, thus states that the claimed methodology is directed to an expression assay as an unambiguous and integral part of the claim.

Thus, Applicants respectfully assert that the Montforte patent neither discloses nor even suggests the methodology of the instant invention.

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn.

The Examiner has rejected claims 1–7 and 10 under 35 U.S.C. § 102(b) as "being anticipated by Wong et al (US 6,120,997, September 19, 2000)".

Specifically, the Examiner states, "Regarding claim 1–3, Wong et al teach a method comprising contacting a target nucleic acid with probe immobilized on a microarray under conditions that allow hybridization, said target nucleic acid having at least one phosphorothioate moiety. Wong et al teach further comprising labeling said target nucleic acid by conjugating a reporter molecule to said phosphorothioate moiety..."

The Examiner continues, "Regarding claim 5–7, Wong et al teach the method of claim 2, wherein said reporter molecule has an electrophilic moiety comprising iodoacetamide..." and, "Regarding claim 10, Wong et al teach wherein at least one nucleotide is a ribonucleotide..."

The Examiner concludes, "Therefore, Wong et al meets the limitations of claims 1–7 and 10 of the instant invention".

In response, Applicants reiterate the arguments presented above regarding the Montforte patent, and respectfully assert that , like the Montforte et al. patent, the Wong et al. patent neither discloses nor even suggests an expression assay as claimed in the captioned application.

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn.

The Examiner has rejected claims 1–8, 12 and 14 under 35 U.S.C. 103(a) as "being unpatentable over Chee et al (WO 98/56954, December 1998) in view of Fidanza et al (Journal of American Chemical Society, Vol. 111, pages 9117-9119) and Housby et al (TIBTECH, vol. 18, pages 439-440, November 2000)".

Specifically, the Examiner states, "Regarding claims 1-8, 12 and 14, Chee et al teach an expression assay, comprising contacting a target nucleic acid with a probe immobilized on an array under conditions that allow hybridization with said target and said probe, said target comprising a label, wherein said label is a florescent label or biotin. Chee et al further teach wherein at least one nucleotide is a ribonucleotide or deoxyribonucleotide and wherein said target is selected from the group consisting of RNA, DNA, cDNA or cRNA...", and continues, "Chee et al differs from the instant invention in that the reference does not teach wherein said target comprises a nucleic acid having at least one phosphorothioate moiety".

The Examiner further continues, "Fidanza et al teach the covalent attachment of reporter groups at specific sites within oligonucleotide sequences using phosphorothioate conjugation with iodacetamide. Fidanza et al teaches that phosphorothioate diesters at

specific sites within DNA fragments can be employed to direct the covalent attachment of reporter groups such as fluorophores spin labels, or drug derivatives to the sugar phosphate backbone. Fidanza et al further teaches that attaching reporter groups (covalently) wherein desired on the DNA backbone allow detailed studies in structure and function and should simplify studies involving protein binding..."

The Examiner further states, "Housby et al provides a general teaching of microarrays and their use in methodologies, which relies on oligonucleotides conjugated with a phosphorothioate moiety. Housby et al teach that an obvious use for microarray technology is in the field of pharmacogenomics. Housby teach that Klaus Giese reported the identification of novel drug target using the proprietary GENEBLOC antisense technology and DNA arrays. Housby et al teach that the inhibitors are oligonucleotides that contain a mixture of 2' methyl ribose and deoxynucleotides with phosphorothioate modification of the phosphate backbone. Housby et al teach that Giese claimed that these molecules are specific for the intended target genes, have low toxicity, are resistant to nuclease and have a high target–binding affinity. Housby et al teach that it was suggested that these molecules might be useful in monitoring gene expression changes during disease progression, and also in studying the effects of gene inhibition on signaling pathways and differential gene expression..."

The Examiner concludes, "One of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the detection method of Chee et al to encompass Fidanza et al's conjugation in order to increase facility of attaching reporter groups for the benefit of studying structure and function of target nucleic acids as suggested by Fidanza et al."

The Examiner further concludes, "One of ordinary skill in the art would have been further motivated to modify the detection method of Chee et al to encompass Fidanza et al's conjugation with a reasonable expectation of success based on the teaching of Housby et al that these molecules are specific for the intended target genes, have a high target–binding affinity and might be useful in monitoring gene expression during disease progression, gene inhibition of pathways and differential gene expression..."

In response, Applicants assert that the Examiner has not properly combined the teachings of the two references to form a rejection under 35 USC § 103(a). Specifically, Applicants point out that WO98/56954 discloses and claims methodology for detecting genetic polymorphisms and monitoring of allelic expressions using a probe array, and acknowledge that the reference does teach that determination of DNA and RNA hybridization profiles, as well as hybridization intensities, can be utilized to characterize specific genotype and/or expression profiles. However, Applicants emphasize that the reference, as the Examiner concedes, does not disclose, nor even suggest, including

phosphorothioate conjugation to allow for the attachment of reporter molecules at various stages within the DNA or RNA molecules.

Applicants further point out that the Fidanza, et al. reference discloses a method of covalently attaching reporter groups at specific sites within DNA sequences, which "would simplify detailed study of the structure and dynamics of unusual DNA forms as well as ligand-DNA or protein-DNA complexes" (see page 9117, lines 1–4); continuing this attachment methodology utilizes a chemistry wherein the phosphorothioate diester will covalently bond to an appropriately labeled reporter group. Applicants further point out that Figure 1 (page 9118) discloses a number of labels which can be attached to the DNA molecule, including a PROXYL spin label, a derivative of dihydropyrroloindole subunits, sulfonamide-linked dansyl fluorophores, and N-linked dansyl fluorophores, and the reference notes that these labeled DNA molecules are quite stable and that structural studies of DNA molecules can be determined.

However, Applicants assert that the Fidanza, et al. reference provides no disclosure, nor even any suggestion, that such methodology would be adaptable, or even useful, in a probe assay of the type disclosed in the '954 PCT publication. Further, Applicants point out that there is no disclosure, nor even any suggestion that the methodology would be useful with RNA expression studies.

Indeed, while the Examiner states that the motivation for combining these references would be "to increase facility of attaching reporter groups", the Fidanza, et al. and Chee et al. references do not, alone or even in combination with each another, remotely suggests that such attachment chemistry would be useful, or even desirable in expression assay methodology.

Applicants further assert that the Examiner has, at best, shown that it would be obvious to try to utilize the attachment chemistry disclosed in the Fidanza, et al. article in the methodology of the Chee et al.PCT publication, inasmuch as the references themselves provide no such teaching; and assert that "obvious to try" is not the proper basis upon which a rejection under 35 U.S.C. § 103(a) can be made.

Applicants further respectfully assert that the Examiner is reading something into the cited references that is neither disclosed nor suggested. More specifically, while Applicants concede that the Chee, et al. application does disclose methodology for the measurement of the expression level of polymorphic forms of a gene using a probe assay, Applicants emphasize that it does not disclose, nor even suggest, the inclusion of a phosphorothioate moiety in the target nucleic acid. Such phosphorothioate moiety will facilitate the attachment of reporter molecules.

Applicants further respectfully submit that while the Fidanza, et al. reference does disclose a method for attaching reporter groups to a DNA sequence utilizing phosphorothioate diesters, it does not disclose including the same in RNA, which would be the target molecules in the expression assay methodology of Chee, et al. Indeed, contrary to the Examiner's statement, which characterizes the teachings of Fidanza, et al. to include "phosphorothioate conjugations to various targets such as cDNA, RNA and DNA", the entire disclosure of the Fidanza, et al. reference is limited solely to the inclusion of the phosphorothioate in DNA only. The other targets the Examiner states are taught by the reference are, Applicants respectfully assert, neither disclosed nor even suggested.

Thus, Applicants dispute the Examiner's statement that the disclosure of Fidanza, et al. would lead the skilled artisan to have a "reasonable expectation of success" that the disclosure of the Fidanza, et al. reference (phosphorothioate conjugation with DNA) could be combined with the expression (RNA) assay of the Chee, et al. disclosure. Indeed, absent the teaching of the use of the material with RNA, Applicants respectfully submit all the examiner has shown is that it would be "obvious to try" to combine the two teachings. Such, Applicants respectfully reiterate, is the not the proper foundation for a rejection under 35 U.S.C. § 103(a) to be made.

With regard to the Examiner's statement that Housby provides "a reasonable expectation of success...that these molecules are specific for the intended target genes, have a high target–binding affinity and might be useful in monitoring gene expression during disease progression, gene inhibition of pathways and differential gene expression", Applicants respectfully assert that the Housby reference neither discloses nor even suggests the same compositions as the Chee, et al. and Fidanza, et al. references. While the compounds disclosed have some similarity to those of Chee et al. and Fidanza et al., Applicants respectfully submit that there is no basis upon which to believe that the compositions would behave identically. As such, Applicants respectfully assert one skilled in the art would not be led to believe that the teachings of Chee, et al. and Fidanza, et al. could be extended as the Examiner has suggested. It is only with the teachings of the instant invention, as presented in the captioned application, that such is seen.

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn.

The Examiner has rejected Claim 9 under 35 U.S.C. § 103(a) as "being unpatentable over Chee et al in view of Fidanza et al and Housby et al as applied to claims 1–8, 12 and 14 above, and further in view Karger et al (US 5,348,633,September 20, 1994)".

Specifically, the Examiner states, "Regarding claim 9, Chee et al in view of Fidanza et al and Housby et al teach an expression assay and an array with probes which binds to labeled target nucleic acids, wherein said labeling comprises conjugating a reporter molecule (e.g., fluorophore) to a phosphorothioate moiety attached to the target. The references differ from the instant invention in that they do not teach wherein said reporter molecule is TMR–maleimide, TMR–iodoacetamide or ALEXAFLUOR–maleimide".

The Examiner continues, "Karger et al discloses et al use of reporter molecules in methods of labeling target molecules. Karger et al teach that a useful reporter molecule should possess strong absorbance and high fluorescence yield in order to produce a measurable signal during analysis. Karger et al further teach that the fluorophore should not photobleach significantly during the method of detection and should be pH insensitive. Karger et al teach that the preferred reporter molecules as fluorescent labeling groups are tetramethylrhodamine iodoacetamide..."

The Examiner concludes, "One of ordinary skill in the art would have been motivated to have modified the detection method of Chee et al in view of Fidanza et al and Housby to encompass the use of the reporter molecule, tetramethylrhodamine iodoacetamide as the labeling group based on the characteristics and advantages taught

by Karger et al that a molecule, such tetramethylrhodamine iodoacetamide possess strong absorbance, high fluorescence yield and produce a measurable signal during analysis".

In response, Applicants reiterate the arguments presented above as to the inapplicability of the Chee, et al., Fidanza, et al. and Housby, et al. references, and respectfully assert that the addition of Karger, et al. does nothing to remedy these deficiencies.

Indeed, the Karger, et al. reference does disclose useful reporter molecules, but does not disclose the methodology of the instant invention, which is only obtained through the teachings of the instant application.

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn.

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn. Applicants believe that the claims, as amended, are in allowable form and earnestly solicit the allowance of claims 1–14.

Respectfully submitted,

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